Form PTO 1390 (REV 5-93) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED / ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		P32292 U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5) 10/048123
INTERNATIONAL APPLICATION NO. PCT/GB00/01520	INTERNATIONAL FILING DATE 19 April 2000	PRIORITY DATE CLAIMED 23 April 1999
TITLE OF INVENTION POLYMORPH OF 5-[4-[2-(N-METHYL-N-(2-PYRIDYL)AMINO)ETHOXY]BENZYL]-THIAZOLIDINE-2,4-DIONE, MALEIC ACID SALT		
APPLICANT(S) FOR DO/EO/US Paul David James BLACKLER, Christine Marie BROWNE, Timothy G. COAKLEY, Robert Gordon GILES and Gilliam MORRISSEY		

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1 [x] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. [x] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. [x] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. [x] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [x] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).

6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [x] have not been made and will not be made.

8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S. C. 371(c)(3)).

9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. [x] An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98; and Form PTO-1449.

12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. 3.28 and 3.31 is included.

13. [x] A FIRST preliminary amendment.

14. [ ] A SECOND or SUBSEQUENT preliminary amendment.

15. [x] Please amend the specification by inserting before the first line the sentence: This is a 371 of International Application PCT/GB00/01520, filed 19 April 2000.

16. [ ] A substitute specification.

17. [ ] A change of power of attorney and/or address letter.

18. [x] An Abstract on a separate sheet of paper.

19. [ ] Other items or information:

US APPLICATION NO. (if known see 37 CFR 1.50)	INTERNATIONAL APPLICATION NO.	ATTORNEYS DOCKET NO.
10/048123	PCT/GB00/01520	P32292

20. [X] The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 C.F.R. 1.492(a)(1)-(5)):		
Search Report has been prepared by the EPO or JPO **$890.00**	**$890.00**	
International Preliminary Examination Fee paid to USPTO (37 CFR 1.492) **$710.00**		
No International Preliminary Examination Fee paid to USPTO (37 CFR 1.492) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) **$740.00**		
Neither International Preliminary Examination Fee (37 CFR 1.492) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....**$1,040.00**		
International Preliminary Examination Fee paid to USPTO (37 CFR 1.492) and all claims satisfied provisions of PCT Article 33(2)-(4).....**$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$890.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	**$0.00**	

Claims	Number Filed	Number Extra	Rate		
Total claims	**11 - 20 =**	**0**	**0 x $18.00**	**$0.00**	
Independent claims	**3 - 3 =**	**0**	**0 x $84.00**	**$0.00**	
Multiple dependent claims (if applicable)			**+ $280.00**	**$0.00**	
TOTAL OF ABOVE CALCULATIONS =				**$890.00**	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				**$**	
SUBTOTAL =				**$890.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)) +				**$**	
TOTAL NATIONAL FEE =				**$890.00**	
				Amount to be refunded	**$**
				charged	**$**

a. ☐ A check in the amount of $____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 19-2570 in the amount of **$890.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-2570 . A duplicate copy of this sheet is enclosed.

d. ☒ General Authorization to charge any and all fees under 37 CFR 1.16 or 1.17, including petitions for extension of time relating to this application (37 CFR 1.136 (a)(3)).

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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33,797
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"EXPRESS MAIL CERTIFICATE"
"EXPRESS MAIL" MAILING LABEL NUMBER EL808220358US
DATE OF DEPOSIT 22 OCTOBER 2001

Attorney Docket No. P32292

INTERNATIONAL APP. NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB00/01520	19 April 2000	23 April 1999

TITLE OF INVENTION
POLYMORPH OF 5-[4-[2-(N-METHYL-N-(2-PYRIDYL)AMINO)ETHOXY]BENZYL]-THIAZOLIDINE-2,4-DIONE, MALEIC ACID SALT

APPLICANT(S) FOR DO/US
Paul David James BLACKLER, Christine Marie BROWNE, Timothy G. COAKLEY, Robert Gordon GILES and Gillian MORRISSEY

PRELIMINARY AMENDMENT

Preliminary to the examination of this application, Applicants respectfully request amendment of the above-identified application as follows:

In the Specification:

Kindly add the Abstract enclosed herewith on a separate sheet, at the end.

In the Claims:

Please cancel claims 11-13.

Please amend claims 1, 3-8 and 14 as follows:

1. (Amended) A polymorphic form of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt (the Polymorph) comprising:

(i) an infra red spectrum containing peaks at 1763, 912, 856 and 709 cm^{-1}; and/or

(ii) a Raman spectrum containing peaks at 1762, 1284, 912 and 888 cm^{-1}; and/or

(iii) a solid-state ^{13}C nuclear magnetic resonance spectrum containing peaks at 111.0, 113.6, 119.8, 129.1, 130.9, 131.8, 134.7, 138.7, 146.5, 152.7, 157.5, 169.5. 171.0, 178.7 ppm; and/or

(iv) an X-ray powder diffraction (XRPD) pattern which gives calculated lattice spacings at 5.87, 5.30, 4.69, 4.09, 3.88, 3.61, 3.53 and 3.46 Angstroms.

3. (Amended) A Polymorph according to claim 1, which provides a Raman spectrum substantially in accordance with Figure II.

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4. (Amended) A Polymorph according to claim1, which provides a solid-state ^{13}C nuclear magnetic resonance spectrum substantially in accordance with Figure III and/or Table I.

5. (Amended) A Polymorph according to claim 1, which provides an X-ray powder diffraction (XRPD) pattern substantially in accordance with Figure IV and/or Table II.

6. (Amended) A Polymorph according to claim 1, in isolated form.

7. (Amended) A Polymorph according to claim 1, in pure form.

8. (Amended) A Polymorph according to claim 1, in crysalline form.

14. (Amended) A method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of Polymorph according to claim 1 to a human or non-human mammal in need thereof.

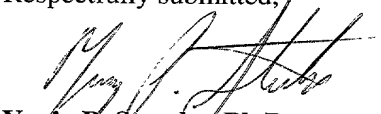
REMARKS

The above-identified application is being entered into the National Phase from PCT application No. PCT/GB00/01520.

Applicants have amended the claims to put them in conformity with U.S. practice. Attached hereto is a marked up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

No new matter has been introduced.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

An abstract has been added.

In the Claims:

Claims 11-13 have been cancelled.

1. (Amended) A polymorphic form of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt (the Polymorph) [characterized in that it provides:] comprising:

comprising:

(i) an infra red spectrum containing peaks at 1763, 912, 856 and 709 cm^{-1}; and/or

(ii) a Raman spectrum containing peaks at 1762, 1284, 912 and 888 cm^{-1}; and/or

(iii) a solid-state ^{13}C nuclear magnetic resonance spectrum containing peaks at 111.0, 113.6, 119.8, 129.1, 130.9, 131.8, 134.7, 138.7, 146.5, 152.7, 157.5, 169.5. 171.0, 178.7 ppm; and/or

(iv) an X-ray powder diffraction (XRPD) pattern which gives calculated lattice spacings at 5.87, 5.30, 4.69, 4.09, 3.88, 3.61, 3.53 and 3.46 Angstroms.

3. (Amended) A Polymorph according to claim 1 [or claim 2], which provides [provides] a Raman spectrum substantially in accordance with Figure II.

4. (Amended) A Polymorph according to [any one of] claim[s] 1 [to3], which provides a solid-state ^{13}C nuclear magnetic resonance spectrum substantially in accordance with Figure III and/or Table I.

5. (Amended) A Polymorph according to [any one of] claim[s] 1 [to 3], which provides an X-ray powder diffraction (XRPD) pattern substantially in accordance with Figure IV and/or Table II.

6. (Amended) A Polymorph according to [any one of] claim[s] 1 [to 5], in isolated form.

7. (Amended) A Polymorph according to [any one of] claim[s] 1 [to 6], in pure form.

8. (Amended) A Polymorph according to [any one of] claim[s] 1 [to 7], in crysalline form.

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14. (Amended) A method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of Polymorph according to claim 1 to a human or non-human mammal in need thereof.

POLYMORPH OF 5-[4-[2-(N-METHYL-N-(2-PYRIDYL)AMINO)ETHOXY]BENZYL]THIAZOLIDINE-2,4-DIONE, MALEIC ACID SALT

This invention relates to a novel pharmaceutical, to a process for the preparation of the pharmaceutical and to the use of the pharmaceutical in medicine.

International Patent Application, Publication Number WO94/05659 discloses certain thiazolidinedione derivatives having hypoglycaemic and hypolipidaemic activity including 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt (hereinafter also referred to as "Compound (I)").

International Patent Applications, Publication Numbers WO99/31093, WO99/31094 and WO99/31095 each disclose distinct hydrates of Compound (I).

It has now been discovered that Compound (I) exists in a novel polymorphic form which is particularly suitable for bulk preparation and handling. The novel form can be prepared by an efficient, economic and reproducible process particularly suited to large-scale preparation.

The novel polymorphic form ('the Polymorph') also has useful pharmaceutical properties and in particular it is indicated to be useful for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

Accordingly, the present invention provides a polymorphic form of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt characterised in that it:

(i) provides an infra red spectrum containing peaks at 1763, 912, 856 and 709 cm^{-1}; and/or

(ii) provides a Raman spectrum containing peaks at 1762, 1284, 912 and 888 cm^{-1}; and/or

(iii) provides a solid-state ^{13}C nuclear magnetic resonance spectrum containing peaks at 111.0, 113.6, 119.8, 129.1, 130.9, 131.8, 134.7, 138.7, 146.5, 152.7, 157.5, 169.5, 171.0, 178.7 ppm; and/or

(iv) provides an X-ray powder diffraction (XRPD) pattern which gives calculated lattice spacings at 5.87, 5.30, 4.69, 4.09, 3.88, 3.61, 3.53 and 3.46 Angstroms.

In one favoured aspect, the Polymorph provides an infrared spectrum substantially in accordance with Figure I.

In one favoured aspect, the Polymorph provides a Raman spectrum substantially in accordance with Figure II.

In one favoured aspect, the Polymorph provides a solid-state nuclear magnetic resonance spectrum substantially in accordance with Figure III and/or Table I.

In one favoured aspect, the Polymorph provides an X-ray powder diffraction (XRPD) pattern substantially in accordance with Figure IV and/or Table II.

The present invention encompasses the Polymorph isolated in pure form or when admixed with other materials, for example the known forms of Compound I (or the "Original Polymorph") or any other material.

Thus in one aspect there is provided the Polymorph in isolated form.

In a further aspect there is provided the Polymorph in pure form.

In yet a further aspect there is provided the Polymorph in crystalline form.

The invention also provides a process for preparing the Polymorph, characterised in that Compound (I) is suspended in acetone, preferably under an inert atmosphere such as nitrogen, and stirred at an elevated temperature, preferably reflux temperature, for an extended period of time, for example 17 hours, after which time the Polymorph is isolated from the reaction mixture.

In an alternative process a solution of Compound (I) in denatured ethanol at an elevated temperature, for example 50°C, is seeded with crystals of the Polymorph then cooled, preferably to a temperature in the range of from 20-25°C, so as to provide the Polymorph, after which time the Polymorph is recovered from the denatured ethanol. The solution of Compound (I) in the denatured ethanol is conveniently prepared by dissolving Compound (I) in the required amount of denatured ethanol at an elevated temperature, for example 60°C.

Typically the Polymorph is recovered from the reaction by filtration and subsequent drying, usually at an elevated temperature, for example 50°C.

In a further aspect, the invention provides a process for converting Polymorph to Compound (I), wherein a solution of Polymorph in a suitable solvent, such as acetone or ethanol, is seeded with Compound (I). Generally, the solution of Polymorph is obtained by dissolving Polymorph at an elevated temperature in the solvent, such as acetone or ethanol.

Compound (I) is prepared according to known procedures, such as those disclosed in WO94/05659. The disclosures of WO94/05659 are incorporated herein by reference.

For the avoidance of doubt the term "Compound (I)" as used herein refers to the form of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt as disclosed an characterised in International Patent Application, Publication Number WO94/05659.

When used herein "denatured ethanol" means ethanol containing small amounts of methanol, usually up to 5% v/v of methanol, such as from 0.9% v/v to 5% v/v of methanol, for example ethanol containing 4%v/v of methanol.

When used herein the term 'prophylaxis of conditions associated with diabetes mellitus' includes the treatment of conditions such as insulin resistance, impaired glucose tolerance, hyperinsulinaemia and gestational diabetes.

Diabetes mellitus preferably means Type II diabetes mellitus.

Conditions associated with diabetes include hyperglycaemia and insulin resistance and obesity. Further conditions associated with diabetes include hypertension, cardiovascular disease, especially atherosclerosis, certain eating disorders, in particular the regulation of appetite and food intake in subjects suffering from disorders associated with under-eating, such as anorexia nervosa, and disorders associated with over-eating, such as obesity and anorexia bulimia. Additional conditions associated with diabetes include polycystic ovarian syndrome and steroid induced insulin resistance.

The complications of conditions associated with diabetes mellitus encompassed herein includes renal disease, especially renal disease associated with the development of Type II diabetes including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

As mentioned above the compound of the invention has useful therapeutic properties: The present invention accordingly the Polymorph for use as an active therapeutic substance.

More particularly, the present invention provides the Polymorph for use in the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

The Polymorph may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier. The formulation of the Polymorph and dosages thereof are generally as disclosed for Compound (I) in International Patent Application, Publication Number WO94/05659 or WO98/55122.

Accordingly, the present invention also provides a pharmaceutical composition comprising the Polymorph and a pharmaceutically acceptable carrier therefor.

The Polymorph is normally administered in unit dosage form.

The active compound may be administered by any suitable route but usually by the oral or parenteral routes. For such use, the compound will normally be employed in the form of a pharmaceutical composition in association with a pharmaceutical carrier, diluent and/or excipient, although the exact form of the composition will naturally depend on the mode of administration.

Compositions are prepared by admixture and are suitably adapted for oral, parenteral or topical administration, and as such may be in the form of tablets,

capsules, oral liquid preparations, powders, granules, lozenges, pastilles, reconstitutable powders, injectable and infusable solutions or suspensions, suppositories and transdermal devices. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

Solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the active compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the active compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the active compound.

In addition such compositions may contain further active agents such as anti-hypertensive agents and diuretics.

In addition, the Polymorph may be used in combination with other antidiabetic agents such as insulin secretagogues, for example sulphonylureas, biguanides, such as metformin, alpha glucosidase inhibitors, such as acarbose, beta agonists, and insulin such as those disclosed in WO98/57649, WO98/57634, WO98/57635 or WO98/57636. The other antidiabetic agents, the amounts thereof and methods of administration are as described in the above mentioned publications. The formulation of the Polymorph and dosages thereof in said combinations are generally as disclosed for Compound (I) in the above mentioned publications.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

As used herein the term 'pharmaceutically acceptable' embraces compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

The present invention further provides a method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of the Polymorph to a human or non-human mammal in need thereof.

Conveniently, the active ingredient may be administered as a pharmaceutical composition hereinbefore defined, and this forms a particular aspect of the present invention.

In the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof the Polymorph may be taken in doses, such as those described above.

Similar dosage regimens are suitable for the treatment and/or prophylaxis of non-human mammals.

In a further aspect the present invention provides the use of the Polymorph for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

No adverse toxicological effects are indicated in the above mentioned treatments for the compounds of the invention.

The following example illustrates the invention but do not limit it in any way.

Example 1: Preparation of Polymorph
Compound (I) (8.0 g) was suspended in acetone (80 ml) under nitrogen and the resulting slurry was stirred at reflux for 17.5 h. The mixture was then cooled to ambient and stirred for 30 min. The product was isolated by filtration, washed with acetone and dried *in vacuo* at 50°C to give 6.9 g (86%) of the Polymorph.

Example 2: Conversion of Polymorph to Compound (I)
Polymorph (18.0 g) was added to acetone (450 ml) and the resultant mixture was heated at reflux under nitrogen for 30 min. The hot solution was filtered, and the filtered solution was concentrated by distillation at atmospheric pressure (270 ml of acetone was collected). The concentrated solution was then allowed to cool at about 1°C/min and at 50°C the solution was seeded with Compound (I) (0.09 g). Cooling at about 1°C /min was continued. The resulting slurry was stirred for 1 h at ambient temperature, then the solid was isolated by filtration, washed with acetone and dried *in vacuo* at 50°C to give 15.1 g (84%) of Compound (I).

Example 3: Conversion of Polymorph to Compound (I)
A mixture of Polymorph (10.0 g) in denatured ethanol (90 ml) was heated under nitrogen to give a clear solution. The clear solution was stirred at 62°C for 30 min then filtered hot to a vessel preheated to 55°C. The filter was washed with hot denatured ethanol (10 ml). The temperature of the filtrate was adjusted to 60°C before cooling, with stirring, at about 1deg/min. The cooling mixture was seeded at 52°C with Compound (I) (0.4 g) and cooling at 1°C/min with stirring was continued. The resultant slurry was stirred at ambient temperature for 1 h and the solid was isolated by filtration, washed with denatured ethanol and dried *in vacuo* at 50°C to give 8.4 g (84%) of Compound (I).

CHARACTERISING DATA: The following characterising data were generated for the polymorph:

A Infrared
The infrared absorption spectrum of a mineral oil dispersion of the Polymorph was obtained using a Nicolet 710 FT-IR spectrometer at 2 cm^{-1} resolution. Data were digitised at 1 cm^{-1} intervals. The spectrum obtained is shown in Figure I. Peak positions are as follows 1763, 1702, 1643, 1623, 1578, 1542, 1515, 1416, 1356, 1334, 1302, 1284, 1261, 1243, 1224, 1201, 1184, 1179, 1147, 1109, 1081, 1055, 1033, 1015, 975, 959, 912, 888, 856, 833, 798, 776, 759, 744, 722, 709, 651, 617, 604, 596, 581, 539, 524 and 505 cm^{-1}.

B Raman

The Raman spectrum of the Polymorph was recorded through a glass vial using a Perkin Elmer 2000R spectrometer at 4 cm^{-1} resolution and is shown in Figure II (X-axis shows Intensity, Y-axis shows Raman shift cm^{-1}, 1800 - 200 cm^{-1}). Excitation was achieved using a Nd:YAG laser (1064 nm) with a power output of 400 mW. Peak positions are as follows: 1762, 1703, 1613, 1586, 1546, 1469, 1446, 1389, 1333, 1315, 1284, 1264, 1249, 1206, 1181, 1147, 1082, 1035, 1014, 991, 969, 922, 912, 888, 840, 830, 778, 743, 722, 708, 654, 636, 618, 604, 541, 499, 468, 434, 411, 334, 290 and 235 cm^{-1}.

C Solid-State NMR

The 90.56 MHz ^{13}C CP-MAS NMR spectrum for the Polymorph is shown in Figure III. Chemical shifts are tabulated in Table 1. Data were recorded at ambient temperature and 10 kHz spinning frequency on a Bruker AMX360 spectrometer, with 1.6 ms cross polarization, and a repetition time of 15 s. Chemical shifts were externally referenced to the carboxylate signal of a glycine test sample at 176.4 ppm relative to tetramethylsilane, and are regarded as accurate to within +/- 0.5 ppm.

Table I.

^{13}C Chemical Shifts of the Polymorph.

Chemical Shift (ppm)				
38.5	111.0	130.9	146.5	171.0
50.3	113.6	131.8	152.7	178.7
56.9	119.8	134.7	157.5	
66.0	129.1	138.7	169.5	

D X-Ray Powder Diffraction (XRPD)

The XRPD pattern of the Polymorph is shown below in Figure IV and a summary of the XRPD angles and calculated lattice spacings characteristic of the Polymorph is given in Table II.
Data were acquired on a Bruker D8 Advance X-ray diffractometer with theta/theta geometry configured with a Cu anode, primary and secondary Soller slits, a

secondary monochromator, and scintillation detector. The following acquisition conditions were used:

Tube anode:	Cu
Generator tension:	40 kV
Generator current:	40 mA
Start angle:	2.0 °2θ
End angle:	35.0 °2θ
Step size:	0.02 °2θ
Time per step:	2.5 s

Table II.

X-Ray Powder Diffraction Angles and Calculated Lattice Spacings Characteristic of the Polymorph.

Diffraction Angle (°2θ)	Lattice Spacing (Angstroms)
9.9	8.97
12.5	7.07
13.1	6.78
15.1	5.87
15.5	5.72
16.7	5.30
18.9	4.69
20.3	4.38
21.2	4.19
21.7	4.09
22.1	4.02
22.9	3.88
23.4	3.80
23.9	3.72
24.6	3.61
25.2	3.53
25.7	3.46
26.3	3.39
27.1	3.29
27.5	3.25
27.9	3.20
28.7	3.11
29.1	3.07
30.1	2.97
30.5	2.93
30.8	2.91
31.3	2.85
31.7	2.82
32.9	2.72
33.2	2.69
33.8	2.65
34.0	2.64

CLAIMS

1. A polymorphic form of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt (the Polymorph) characterised in that it provides:

(i) an infra red spectrum containing peaks at 1763, 912, 856 and 709 cm^{-1}; and/or

(ii) a Raman spectrum containing peaks at 1762, 1284, 912 and 888 cm^{-1}; and/or

(iii) a solid-state ^{13}C nuclear magnetic resonance spectrum containing peaks at 111.0, 113.6, 119.8, 129.1, 130.9, 131.8, 134.7, 138.7, 146.5, 152.7, 157.5, 169.5, 171.0, 178.7 ppm; and/or

(iv) an X-ray powder diffraction (XRPD) pattern which gives calculated lattice spacings at 5.87, 5.30, 4.69, 4.09, 3.88, 3.61, 3.53 and 3.46 Angstroms

2.. A Polymorph according to claim 1, which provides an infra red spectrum substantially in accordance with Figure I.

3. A Polymorph according to claim 1 or claim 2, which provides provides a Raman spectrum substantially in accordance with Figure II.

4. A Polymorph according to any one of claims 1 to 3, which provides provides a solid-state ^{13}C nuclear magnetic resonance spectrum substantially in accordance with Figure III and/or Table I.

5. A Polymorph according to any one of claims 1 to 3, which provides an X-ray powder diffraction (XRPD) pattern substantially in accordance with Figure IV and/or Table II.

6. A Polymorph according to any one of claims 1 to 5, in isolated form.

7. A Polymorph according to any one of claims 1 to 6, in pure form.

8. A Polymorph according to any one of claims 1 to 7, in crystalline form.

9. A process for preparing a Polymorph according to claim 1, characterised in that either:

(a) Compound (I) is suspended in acetone and stirred at an elevated temperature for an extended period of time; or

(b) Compound (I) in denatured ethanol at an elevated temperature is seeded with crystals of the Polymorph, the reaction mixture is then cooled so as to provide the Polymorph;
after which time the Polymorph is recovered from the denatured ethanol.

10. A pharmaceutical composition comprising an effective, non-toxic amount of a Polymorph according to claim 1 and a pharmaceutically acceptable carrier therefor.

11. A Polymorph according to claim 1, for use as an active therapeutic substance.

12. A Polymorph according to claim 1, for use in the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

13. The use of Polymorph for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

14. A method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of Polymorph to a human or non-human mammal in need thereof.

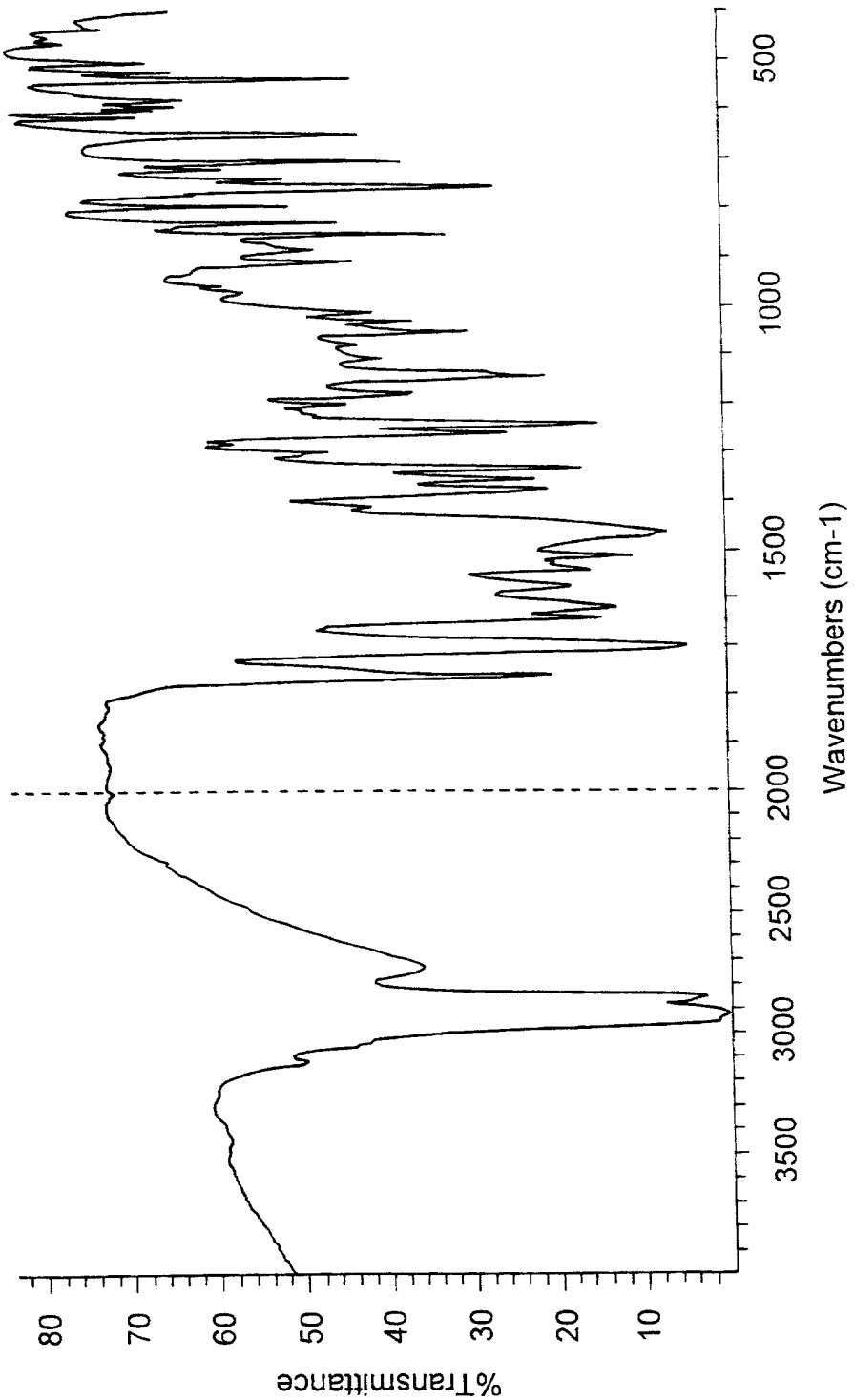

Fig. 1 Infrared Spectrum of the Polymorph

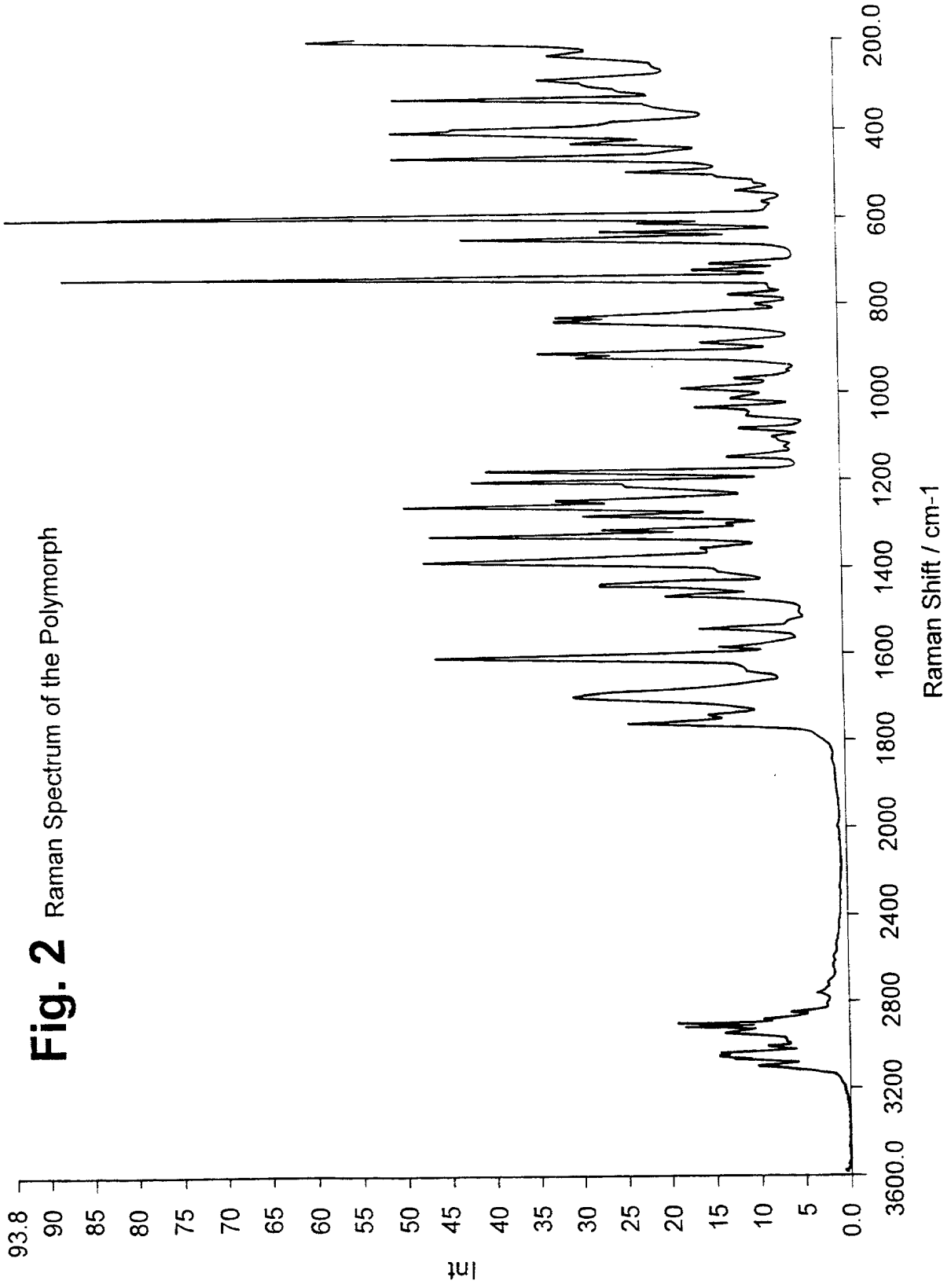
Raman Spectrum of the Polymorph
Int
Raman Shift / cm-1
93.8
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.0
3600.0
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400
200.0

Fig. 2

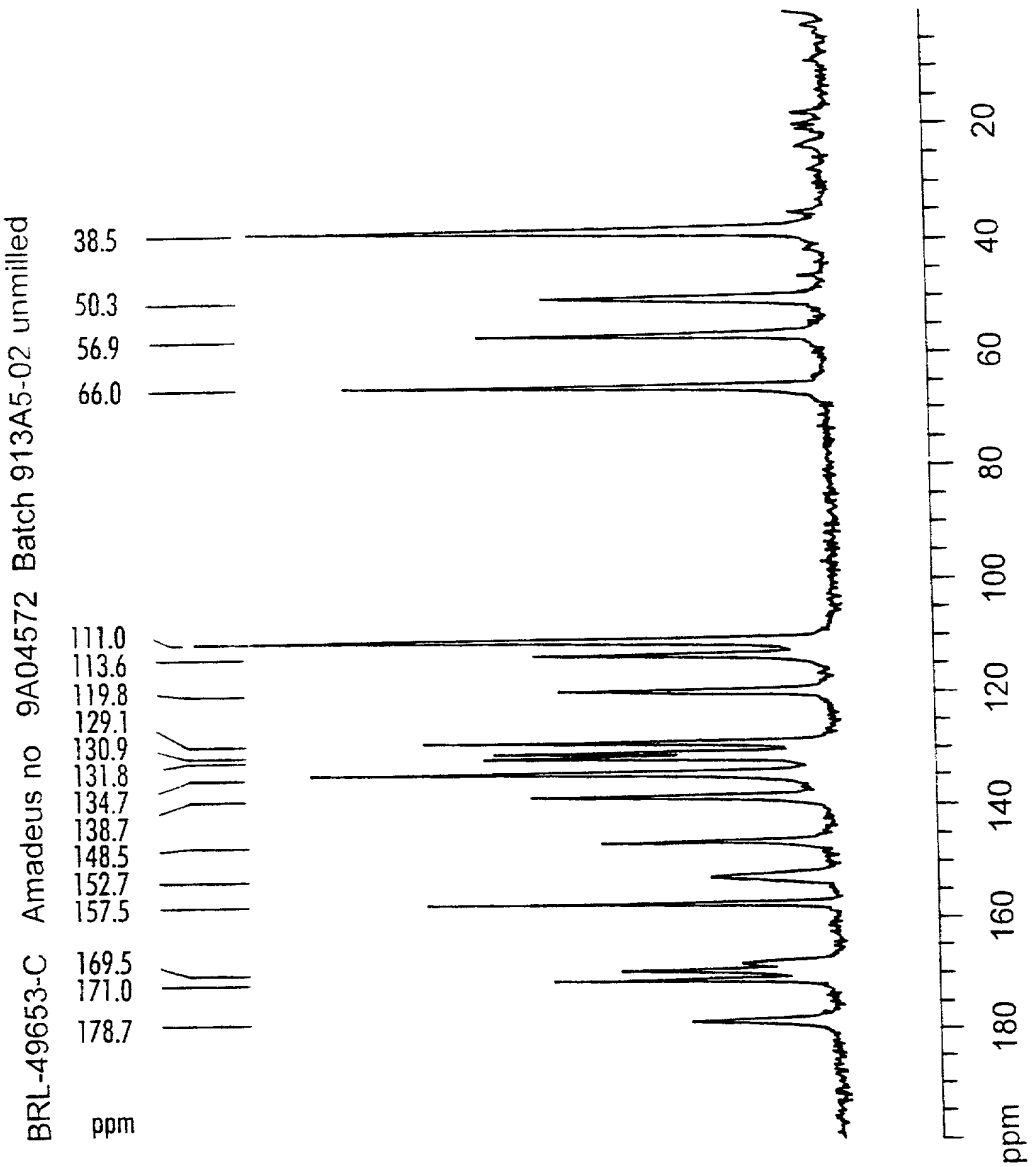

Fig. 3 Solid-State NMR Spectrum of the Polymorph

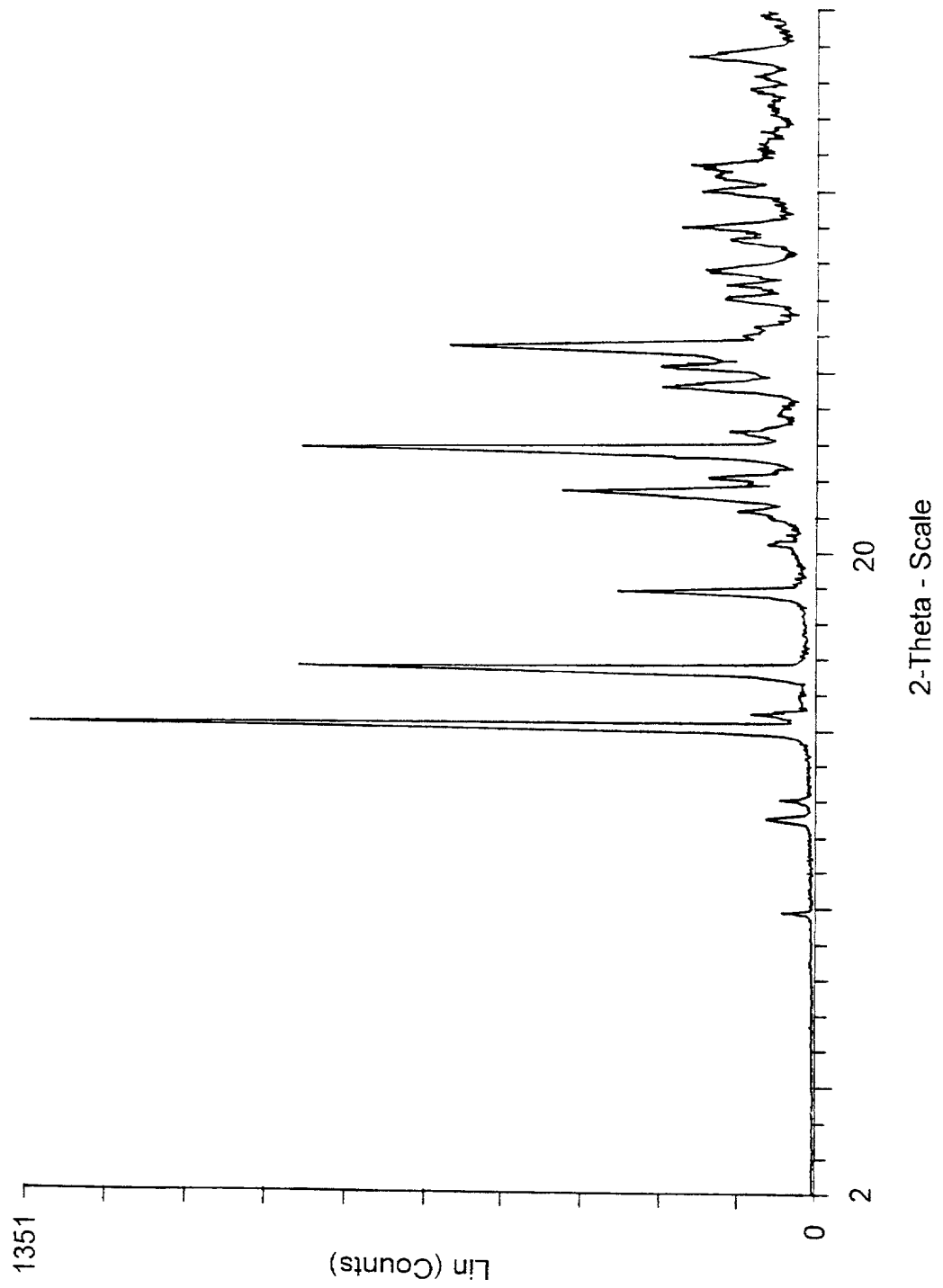

Fig. 4 X-Ray Powder Diffraction Pattern of the Polymorph

Docket No.: P32292 PCT/GB00/01520

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

POLYMORPH OF 5-[4-[2- (N-METHYL-N-(2-PYRIDYL)AMINO) ETHOXY]BENZYL] THIAZOLIDINE-2,4-DIONE, MALEIC ACID SALT

the specification of which (check one)

[ ] is attached hereto.

[X] was filed on 19 April 2000 as Serial No. PCT/GB00/01520
and was amended on (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or Inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Number	Country	Filing Date	Priority Claimed
9909473.2	GREAT BRITAIN	23 April 1999	Yes
9912196.4	GREAT BRITAIN	25 May 1999	Yes

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below.

Application Number	Filing Date

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

Serial No.	Filing Date	Status

I hereby appoint the practitioners associated with the Customer Number provided below to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, and direct that all correspondence be addressed to that Customer Number:

Customer Number 20462.

Address all correspondence and telephone calls to Yuriy Stercho, GlaxoSmithKline, Corporate Intellectual Property-U.S., UW2220, P.O. Box 1539, King of Prussia, Pennsylvania 19406-0939, whose telephone number is 610-270-5018.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issued thereon.

1-00

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5-02

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